Health Policy and Technology 8 (2019) 408–413

Contents lists available at ScienceDirect

Health Policy and Technology

journal homepage: www.elsevier.com/locate/hlpt

The impact of implemented regulations on biosimilars in Slovakia

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ARTICLE INFO

Article history:
Available online 2 October 2019

Keywords:
Biosimilars
Decision making
Health insurance
HTA
Reimbursement
Slovakia

ABSTRACT

Objectives: The aim of this study was to review legislative provisions for the reimbursement of biosimilars, assess the impact of the implemented regulations on access to biosimilars, and to calculate the lost opportunity for savings due to the limited availability of biosimilars in Slovakia.
Methods: The Slovak legislation concerning the reimbursement of biosimilars was reviewed. The reimbursement dossiers of medicines, health technology assessments and appraisals, justification of the reimbursement decisions, final reimbursement decisions and all aspects of the appeal mechanisms are transparently published on the website of the Slovak Ministry of Health (http://kategorizacia.mzsr.sk/Lieky), and these were used for this analysis.
Results: Only 14 reimbursement dossiers were submitted for biosimilars between 2006 and September 2018 in Slovakia. In 2016 and 2017, no reimbursement dossiers were submitted. The results, based on data provided by wholesalers who are legally obliged to deliver information to the State Institute for Drug Control, showed that the Slovak health budget could save €28.26-€39.56 million per year if biosimilars with marketing authorisations were available in the Slovak market, and a 25–35% decrease in price compared with that of biological medicinal products.
Conclusions: Our findings show that proactive strategies and policies should be implemented to increase availability and penetration of biosimilars on the Slovak pharmaceutical market to reduce societal losses that are caused by the lack of biosimilar medicines availability.

Introduction

The Constitution of Slovakia guarantees all residents universal and free access to a wide package of basic health care, covered by the public health insurance system. All residents are insured and are obliged to pay premiums to the public health insurance fund, which is operated by three health insurance companies. The health-care system in Slovakia is based on universal coverage, compulsory health insurance, a basic benefits package and a competitive insurance model, with selective contracting of health-care providers and flexible pricing of health services [1,2]. According to Barnieh et al. the Slovak Republic met the highest standard for the three criteria deemed important in the process of reimbursement for drugs, which are consideration of the clinical and cost evidence, full transparency, and the presence of a formal appeal mechanism [3].

Slovakia has implemented an internal reference pricing system for medicines. Based on this system, a maximum price is set for a standard daily dose of medicine in each specific reference group of medicines. All medicines in each internal reference group (based on the seven-digit Anatomical Therapeutic Chemical Classification System code) contain the same active substance(s) and are administered in the same form. The reimbursement level (in absolute terms) for a standard daily dose of a medicine with the particular active substance(s) is linked to the least expensive alternative in a given internal reference group. A change in a price of a particular medicine can thus influence the reimbursement of other medicines in the same internal reference group. If a biosim-

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https://doi.org/10.1016/j.hlpt.2019.09.004

ilar comes onto the market and into the internal reference group containing a biologic, the reimbursement level of medicines in the internal reference group is determined based on the level of the least expensive alternative in the reference group, which is likely the biosimilar; the biosimilar is then fully reimbursed by health insurance funds in Slovakia. When multiple biosimilars enter the market, the same concept is applied and the reimbursement level is determined based on the level of the least expensive alternative in the internal reference group. Therefore, the other biosimilars and the original biologic are reimbursed at the same reimbursement level (in absolute terms) for the standard daily dose as the least expensive alternative in the internal reference group [1].

The advent of biological medicinal products, i.e., medicines produced by or extracted from a biological source, has revolutionised the treatment of many diseases, owing to the specificity of medicinal products for key disease mediators, e.g. tumour necrosis factor (TNF) alpha, a cytokine involved in the body's inflammatory response [4]. Biosimilar medicines can provide savings to society [5–7]. After marketing authorisation is received from the European Commission, it is the responsibility of member states to co-ordinate pricing, reimbursement and subsequent entry of these products to the market. This approach contributes to variations in the use of biosimilars across Europe [8].

It has been demonstrated that the lowering of drug costs is not just about the use of biosimilars, but also about leveraging the competition to alter the market dynamics between the biosimilar and originator product and associated prices [9]. In lower-income European countries with barriers towards the use of patented biologic treatments, the policy objective of biosimilar medicines is not only to save money, but to increase patient access to biological medicines [10]. Many publications only provide a brief overview of existing policies on biosimilars [11–13]; therefore, many authors have urged that the impact of implemented regulations and practices are studied in a quantitative manner [11,14]. Accordingly, this article provides a review of legislative provisions for the reimbursement of biosimilars, the impact of the implemented regulations on the access to biosimilars, and calculations of the lost opportunity for savings due to the limited availability of biosimilars in Slovakia.

Methodology

The authors focused on the impact of implemented regulations and practices in a quantitative manner. Comparative analysis was performed in three steps: (a) a review of the legislative provisions on biosimilars in Slovakia, (b) comparative analysis of market shares of biological medicinal products and biosimilars and (c) calculation of the lost opportunity for savings due to the insufficient use of biosimilars in Slovakia using two different methods.

The reimbursement dossiers of medicines, health technology assessments and appraisals, justification of reimbursement decisions, final reimbursement decisions and all aspects of appeal mechanisms are transparently published on the website of the Slovak Ministry of Health (http://kategorizacia.mzsr.sk/Lieky) and these were used for this analysis. The reimbursement decisions concerning biosimilars, made by the Slovak Ministry of Health between 2006 and September 2018, were studied. The consumption of biosimilars in 2017 in the Slovak Republic was analysed. Sales data from wholesalers, which are legally obliged to provide information to the State Institute for Drug Control, were used for the analysis. The State Institute for Drug Control is the institution of the state authority in the field of human pharmacy and drug precursors.

A control analysis was performed to validate findings. Data from health insurance funds, which are legally obliged to provide information to the National Health Information Centre, were used. The National Health Information Centre, a state-funded organisation founded by the Ministry of Health of the Slovak Republic, performs tasks in the area of health statistics and provision of library and information services in the field of medical sciences and health services.

Results

Table 1 shows information about the availability of biosimilars in Slovakia in September 2018. It is important to mention that there were 47 biosimilars approved by the European Medicines Agency (EMA) between 2006 and September 2018. In the same period, only 14 reimbursement dossiers were submitted for biosimilars in Slovakia. Since 2012, all reimbursement dossiers for medicines, health technology assessments and appraisals, justifications of reimbursement decisions, final reimbursement decisions and all aspects of appeal mechanisms have been transparently published on the website of the Slovak Ministry of Health. Therefore, in Table 1 we included the exact date of reimbursement decisions concerning biosimilars executed by the Slovak Ministry of Health from 2012 onwards.

Sales data from wholesalers, which are legally obliged to provide information to the State Institute for Drug Control, were used for the analysis of the opportunity cost. The results provided in Table 2 show that the Slovak health budget could save €28.26-€39.56 million per year if biosimilars with marketing authorisation were available in the Slovak market and a 25–35% decrease in price (the latter being based on the study by Simon [15]), compared with that of biological medicinal products (applied as an assumption). The second assumption was that there would be no increase in the consumption of particular biosimilars in Slovakia.

Data from health insurance funds, which are legally obliged to provide information to the National Health Information Centre, were used for the control analysis. The results provided in Table 3 show that the Slovak health budget could save €25.57-€35.80 million per year if biosimilars with marketing authorisation were available on the Slovak market and a 25–35% decrease in price, compared with that of biological medicinal products. It was assumed that there would be no increase in the consumption of particular biosimilars in Slovakia.

Differences between the data from wholesalers of medicinal products and health insurance funds may partly be due to parallel export of medicinal products.

The legislative provisions for biosimilars were reviewed in Slovakia. It is important to emphasise that from 2012 to 2017 the Slovak legislature required a 20% initial price reduction for a new biosimilar compared with the price of the reference biological drug from the same reference groups. There were no new biosimilars coming to the Slovak market in 2016 and 2017. Surprisingly, the Slovak Ministry of Health decided to make entry into the Slovak pharmaceutical market even more difficult for biosimilars. The new legislative decision, which came into force on January 1, 2018, stated that the first biosimilar entering the Slovak market should bring a 30% initial price reduction compared with the price of the reference biological drug (for 2019, the first biosimilar coming to the Slovak market should bring a 25% initial price reduction compared with that of the reference biological drug). The second biosimilar coming to the Slovak market should bring an additional 5% price reduction compared with that of the first biosimilar, and the third should bring an additional 5% price reduction compared with that of the second biosimilar. Manufacturers of biosimilars are obliged to decrease prices for the second and third biosimilars coming to the Slovak market by 5%.

Moreover, an external reference pricing procedure (requiring an average of the three lowest prices for the same medicine available on pharmaceutical markets across the European Union) is applied

Table 1
Availability of biosimilars in Slovakia in September 2018.

Year of marketing authorisation in EMA	Active substance (name of medicinal product)	Marketing authorisation holder	Reimbursement decision of the Slovak Ministry of Health
2006	Somatropin (Omnitrope)	Sandoz	before 2012 Comment: Marketing authorisation holder withdrawn the medicinal product from the reimbursement list 29.11.2013
2007	Epoetin alfa (Binocrit)	Sandoz	before 2012
2008	Filgrastim (Ratiograstim)	Ratiopharm	before 2012
2009	Filgrastim (Zarzio)	Sandoz	before 2012
2013	Filgrastim (Grastofil)	Apotex	01.04.2014
2013	Infliximab (Inflectra)	Hospira	31.10.2013
2013	Infliximab (Remsima)	Celltrion	31.10.2013
2014	Insulin glargine (Abasaglar)	Eli Lilly/Boehringer Ingelheim	31.03.2015
2014	Filgrastim (Accofil)	Accord Healthcare	28.07.2015
2014	Follitropin alfa (Bemfola)	Finox Biotech	01.10.2015
2017	Rituximab (Blitzima)	Celltrion	10.07.2018
2017	Rituximab (Rixathon)	Sandoz	13.08.2018
2018	Trastuzumab (Kanjinti)	Amgen/Allergan	09.08.2018
2017	Trastuzumab (Herzuma)	Celltrion	13.09.2018

Table 2
Estimate of financial savings due to biosimilars, based on data from the State Institute for Drug Control.

Active substance	Financial expenditures for ATC5, 2017 (€)	Penetration of biosimilars as financial expenditures for active substances, 2017 (€)	Penetration of biosimilars as share of financial expenditures of active substances /ATC5, 2017	Estimate of financial saving based on 25–35% decrease in price (mil. €)
Adalimumab	34,277,367	0	0%	8.57–12.00
Bevacizumab	22,280,539	0	0%	5.57–7.80
Infliximab	16,062,325	3065,672	19.09%	0
Trastuzumab	12,727,479	0	0%	3.18–4.45
Rituximab	12,249,874	0	0%	3.06–4.29
Etanercept	11,743,854	0	0%	2.94–4.11
Somatropin	8601,234	0	0%	2.15–3.01
Enoxaparin sodium	8335,371	0	0%	2.08–2.92
Epoetin	7086,830	4824,873	68.08%	0
Insulin glargine	5986,612	1353,104	22.6%	0
Insulin lispro	2173,453	0	0%	0.54–0.76
Filgrastim	1616,607	1604,009	99.22%	0
Follitropin alfa	684,997	63,289	9.24%	0
Teriparatide	639,379	0	0%	0.16–0.22
Total	**144,465,921**	**10,910,947**	**7.55%**	**28.26–39.56**

Table 3
Estimate of financial savings due to biosimilars, based on data from the National Health Information Centre.

Active substance	Financial expenditures for ATC5, 2017 (€)	Estimate of financial saving based on 25–35% decrease in price (mil. €)
Adalimumab	36,810,888	9.20–12.88
Bevacizumab	20,070,324	5.02–7.02
Trastuzumab	11,670,196	2.92–4.08
Etanercept	10,887,585	2.72–3.81
Rituximab	7762,640	1.94–2.72
Somatropin	7012,162	1.75–2.45
Enoxaparin sodium	4038,414	1.01–1.41
Insulin lispro	3209,967	0.54–0.76
Teriparatide	826,476	0.21–0.29
Total	**102,288,653**	**25.57–35.80**

as well. There are cases when a 5% decrease in prices for biosimilars would result in a level below even the average of the three lowest prices of the same medicinal product available on pharmaceutical markets across the European Union. Therefore, the prices of such biosimilars in Slovakia would influence the floor prices in other European countries using the external reference pricing system.

Finally, a problem concerning the new Slovak legislation could be that new types of packages of biosimilars are considered new medicinal products, and the concept of the three-step system for decreasing prices is applied even in this case. For example, when a biosimilar from a marketing authorisation holder consisting of ten injections is available on the National reimbursement list, and the marketing authorisation holder would like to include a biosimilar with the same active substance consisting of five injections, the latter is considered a new biosimilar medicine.

Discussion

Kutzin argued that the main policy objective of health-care decision makers is to maximise the health gain for the population by improving the allocative efficiency of limited resources [16]. The objective of an off-patent drug policy, provided that patients have full access to the respective original products prior to their

patent expiry, is usually defined as a reduction in health expenditure without compromising health outcomes [17].

Results presented in Table 1 show that Slovakia has a significant problem with the availability of biosimilars on the pharmaceutical market. There were not available biosimilars in the following reference groups: epoetin zeta, etanercept, somatropin.

In Slovakia, all biologic and biosimilar medicines in a given reference group have the same level of reimbursement from the health insurance funds, which is equal to the price of the least expensive alternative in the internal reference group. The copayments for all medicines except the least expensive alternative equal the difference between the reimbursement level of the least expensive alternative and the real prices of medicines in the internal reference group. Therefore, although it is the physician's decision to choose the right treatment for a patient, health insurance funds provide the same reimbursement level (in absolute terms) for a standard daily dose of biosimilars or the original biologic in the same internal reference group. Slovakia has a pluralistic system of health insurance companies, with three health insurance companies operating: the state-owned General Health Insurance Company ("Všeobecná zdravotná poist'ovňa") and the private Trust ("Dôvera") and Union, which covered 60.97%, 29.55%, and 9.47% of the Slovak population, respectively, in 2019. The cost-saving potential and the capacity to improve patient access to reimbursed biologics are emphasized as key benefits of increased utilization of biosimilars by health insurance funds in Slovakia. These health insurance funds argue that the same high standards of quality, safety and efficacy are applied for biosimilars and original biologics, and biosimilars have been used safely in the EU since 2006 as alternatives to reference medicines. Although health insurance funds in Slovakia set the reimbursement levels of biosimilars and original biologics, they fully accept that the decision regarding which medicine is the right option for a patient is the responsibility of physicians. Prescribers should select the appropriate product based on sufficient data and knowledge and after informing the patient of any changes (e.g., original biologic to biosimilar, biosimilar to original biologic, or biosimilar to biosimilar). Patient access to high-cost biological medicines in Slovakia is limited because of the need to ensure the sustainability of health care financing in Slovakia. There are financing protocols that allow prescriptions only for subgroups of patients, ensuring reimbursement for second-line therapy only after the first-line therapy fails, the provision of prescriptions for second-line therapy is limited to selected centers.

The first tender for infliximab (based on the active substance) was organized by the General Health Insurance Company in 2018. The winner of the tender was able to decrease the price by 57% compared to the official reimbursement level for the standard daily dose of medicines with the same active substance, which was linked to the least expensive alternative in the internal reference group according to the national reimbursement list. The winner of the tender volume-based agreement regarding infliximab was not declared in the contract with the General Health Insurance Company. After the tender, the marketing authorization holders related to the rest of the biosimilars (with infliximab as the active substance) and the original biologic decreased their prices to the same level as the winner. Therefore, there were multiple medicines with infliximab as the active substance that had a price of 57% lower than the original reimbursement level for a standard daily dose of medicine in the internal reference group for infliximab. As the Slovak health insurance funds covered all medicines containing infliximab as the active substance at the same reimbursement level (that of the least expensive alternative in the internal reference group), the winner of the tender did not increase its market share of the Slovak pharmaceutical market.

A second tender was organized by the General Health Insurance Company in 2019 for rituximab. However, because the marketing authorization holders learned from the first tender that there would be no volume-based agreement, the winner only offered a 25% lower price compared to the official reimbursement level for the standard daily dose of medicine in the internal reference group for rituximab.

Results presented in Table 2 show that there were low penetrations of biosimilars in the following reference groups: follitropin alfa, infliximab and insulin glargin. It means that physicians have also big influence on the low level of usage of biosimilars. This can also lead to low interest of manufacturer to launch new biosimilar drugs in Slovakia. On the other hand, there were high penetrations of biosimilars in the following reference groups: epoetin and filgrastim.

Some authors argue that in countries with restricted or no access to original biological medicines, the main benefit of biosimilars is not related to their cost-saving potential and the main objective of biosimilar policies has to be defined from an investment perspective [18,19] by improving patient access via increasing the number of treated patients [10,20]. However, in Slovakia originals are available and standardly used for all active substances where biosimilars are available too.

Despite the application of rigorous criteria, a potential concern about biosimilars is the extrapolation of clinical data required for registration to all indications of the original product [21].

A systematic literature review found that biosimilar immunogenicity differs among active compounds suggesting that immunogenicity of anti-drug antibodies should be an important consideration in the treatment decision-making process such as switching [22].

Some authors argue that switching from an original biologic medicine to a biosimilar may induce increased immunogenic reactions [23,24].

Recent systematic reviews showed, however, that switching patients from the original chronic biologic therapy to a biosimilar alternative was not associated with increased risk of adverse reactions or loss of efficacy [25,26].

Still, even with these recent findings, the utilisation of biosimilars, especially for patients on maintenance original biologic treatment, is not an obvious alternative for many physicians [27–30].

Some authors argue that information that clinicians deem important to assess, such as safety, efficacy and cost, will need to be provided before they are comfortable prescribing biosimilars [31].

Findings from a recently published systematic review indicate that clinicians in Europe and the US do not primarily support the use of biosimilars as safe and effective therapies in patients already receiving originator biological treatment [32].

The results of a survey carried out by the European Society for Medical Oncology (ESMO) on biosimilars understanding in oncologists have highlighted the need for education and worldwide alignment [33].

The current knowledge and perception among different clinicians in Slovakia regarding biosimilars in comparison with original biologics is unknown. The scarcity of this information in Slovakia represents a limitation of our study, which will be alleviated by the publication of the results of an ongoing analysis.

There is no doubt that the evolution of the uptake of biosimilars depends on the perception of clinicians, who act as opinion leaders, as well. In Norway key opinion leaders envisaged first-line use of biosimilar medicines for biologic naïve patients in inflammatory bowel disease [34]. In Denmark, similar approach has been facilitated by the national council for expensive hospital medicines in rheumatology and gastroenterology [11,35]. The current thinking of Swedish specialists prescribing TNFα inhibitors seems to be in line with the position statement of the Swedish Medical Products Agency, which deems treatment with a biosimilar uncontroversial in treatment-naïve patients and believes no barriers exist to switch

stable, well-informed patients from the originator biological to the biosimilar. The position statement also indicates that more data are needed on multiple switching [9].

Clinicians acting as opinion leaders in the European Crohn's and Colitis Organisation (ECCO) published that switching from the originator to a biosimilar in patients with inflammatory bowel disease is acceptable [36]. Statements such as this can significantly influence clinicians, who act as opinion leaders, in Slovakia.

Despite of the underuse of biosimilar medicines, in a recent legislative amendment Slovakia has increased entry barriers for biosimilars by requiring significant initial price reductions. At the same time, Slovakia has reduced the hurdles of including innovative medicines to the reimbursement list.

Slovakian reimbursement decisions from 2012 to 2017 were based on thresholds (commonly described with the Greek letter "λ") set out in Act No. 363/2011 Z. z that were based on cost and quality-adjusted life year (QALY). The lower threshold (λ1) was defined as 24 times average monthly salary (21,192 EUR/QALY), and the upper threshold (λ2) was defined as 35 times average monthly salary (30,905 EUR/QALY). The medicine was reimbursed from the public health insurance fund (fully or partially) if the incremental cost was lower or equal to λ1 per QALY. The medicine was conditionally reimbursed if the incremental cost was between the λ1 and λ2 thresholds per QALY. Medicinal products with additional costs per QALY that exceeded the upper λ2 threshold should not have been included in the reimbursement list.

New legislation (updated Act No. 363/2011 Z. z.) came into force on January 1, 2018, stipulating that reimbursement were to be based on the following thresholds:

- the lower threshold (λ_1): 35 times average monthly salary (total 31,920 EUR/QALY);
- the upper threshold (λ_2): 41 times average monthly salary (total 37,392 EUR/QALY) [37].

In general, a medicinal product is reimbursed from the public health insurance fund (fully or partially) if the incremental cost is lower or equal to λ_1 per incremental QALY. In defined cases, the thresholds per incremental QALY can be increased up to λ_2. Decree No. 93/2018 of the Ministry of Health of the Slovak Republic sets out the method for determining the impact of a medication on the public health insurance funds budget, the evaluation criteria for the calculation of the threshold value coefficient, and how this is calculated [38]. The criteria considered for the threshold increase up to λ_2 are as follows:

- Positive recommendations from agencies responsible for health technology assessments (HTA) in France, Germany, Scotland, and England, or the medicinal product is already covered by health-care funds in France, Germany, Scotland, and England.
- Availability of other medicinal products with marketing authorisations for the same therapeutic indication.
- The budget impact for 12 months after incorporation of a medicinal product into the national reimbursement list.
- The level of incremental QALY brought by a new medicinal product.
- Orphan designation given to a medicinal product.

The HTA agencies included in the legislation are from high-income countries. It is important to point out that what is cost effective in these countries, at international price levels, may not necessarily be cost effective in Slovakia. Van Wilder et al. point out that the thresholds for incremental costs per QALY introduce a cost-effectiveness assessment tool for drugs in Slovakia rather than a reimbursement exclusion regulation [39].

Despite higher cost-effectiveness thresholds that give easier market access to innovative medicines, increased hurdles to market entry for biosimilars mean that the biologic arena is less competitive and price erosion is minimal. Off-patent biopharmaceuticals therefore may not be able to deliver the expected savings for the pharmaceutical budget.

The following proposal, prepared by the Institute of Health Policies from the Slovak Ministry of Health, to support the biosimilar policy in Slovakia is under discussion:

1. Health insurance funds will define targets for switching from an original biologic to a biosimilar for each original biologic with a biosimilar alternative for 3, 12 and 24 months after a new biosimilar comes onto the market and the criteria for treatment-naive patients.
2. Targets will be defined as percentage change from the total number of patients taking the original biologic based on a particular indication.
3. These targets will be included in contracts between health care providers and health insurance funds.
4. The Ministry of Health will support the process by issuing a directive to the General Health Insurance Company (state owned) and the state health care providers.
5. Financial incentives will be considered to remunerate health care providers for achievements of the targets.

Conclusions

We observed that Slovakia has a significant problem with the availability and penetration of biosimilars on the pharmaceutical market. A national agreement among the Ministry of Health, associations of health care providers, hospital organizations, the pharmaceutical industry, and health insurance funds should be reached in this field.

Author statements

Funding: Tomas Tesar, Andras Inotai, Pawel Kawalec and Martin Wawruch declare that they have no received any funding for their work on collection, analysis and interpretation of data and writing of the manuscript. Peter Golias received research grant for calculation of the lost opportunity for savings from the Association of generic drug manufacturers in Slovakia. Peter Golias declares that he has not received any funding for writing of the manuscript.

Competing interests: None declared

Ethical approval: Not required

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